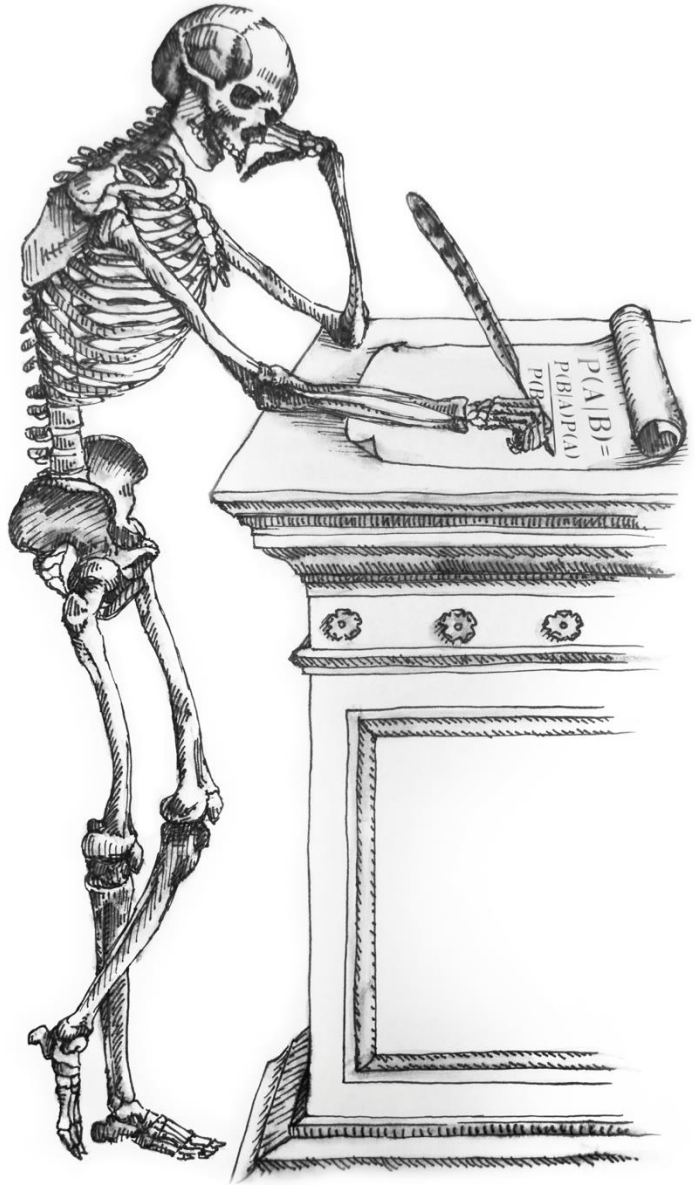

Medicolegal Causation of Suicide

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Disclaimer

The following lecture is for internal U.S. Department of Veterans Affairs educational purposes only.

The views expressed are those of the authors and do not reflect the official policy or position of VA or the U.S. government.

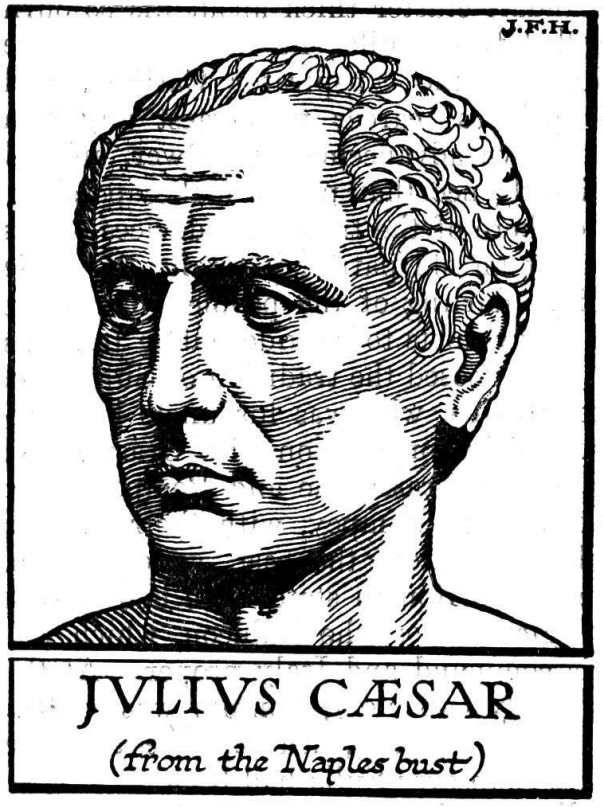
Dr. Michael Freeman has reported that he is a forensic consultant for Forensic Research and Analysis. The planning committee found no conflict of interest.

References in this training to any specific commercial product, process, or service or the use of any trade, firm, or corporation name are for the information and convenience of the training attendees and do not constitute endorsement, recommendation, or favoring by VA.

Presentation goals

- Describe injury causation methods for forensic investigation of suicide
  - Plausibility
  - Temporality
  - Alternative explanations
- Standards for legally admissible opinion
- Suicide case presentation
  - teen suicide following exposure to mis-dispensed drug

The term “Forensic” originated with the death of Julius Caesar, in 44 BC



A Roman physician claimed to be able to determine which stab wound was the fatal one

The Roman Forum [ca. 179 AD]

Today's "forum"

Causation is a key part of criminal and civil cases of injury and death

- All cases require evidence of harm to an individual or group be established
  - Injury and death, acute and chronic illness
- All cases require evidence of wrongful action on the part of a defendant
  - Harm is due to actions *committed* or *omitted*
- Causation is the medical opinion linking the harm and the wrongful action
- Courts require "reasonable medical certainty"

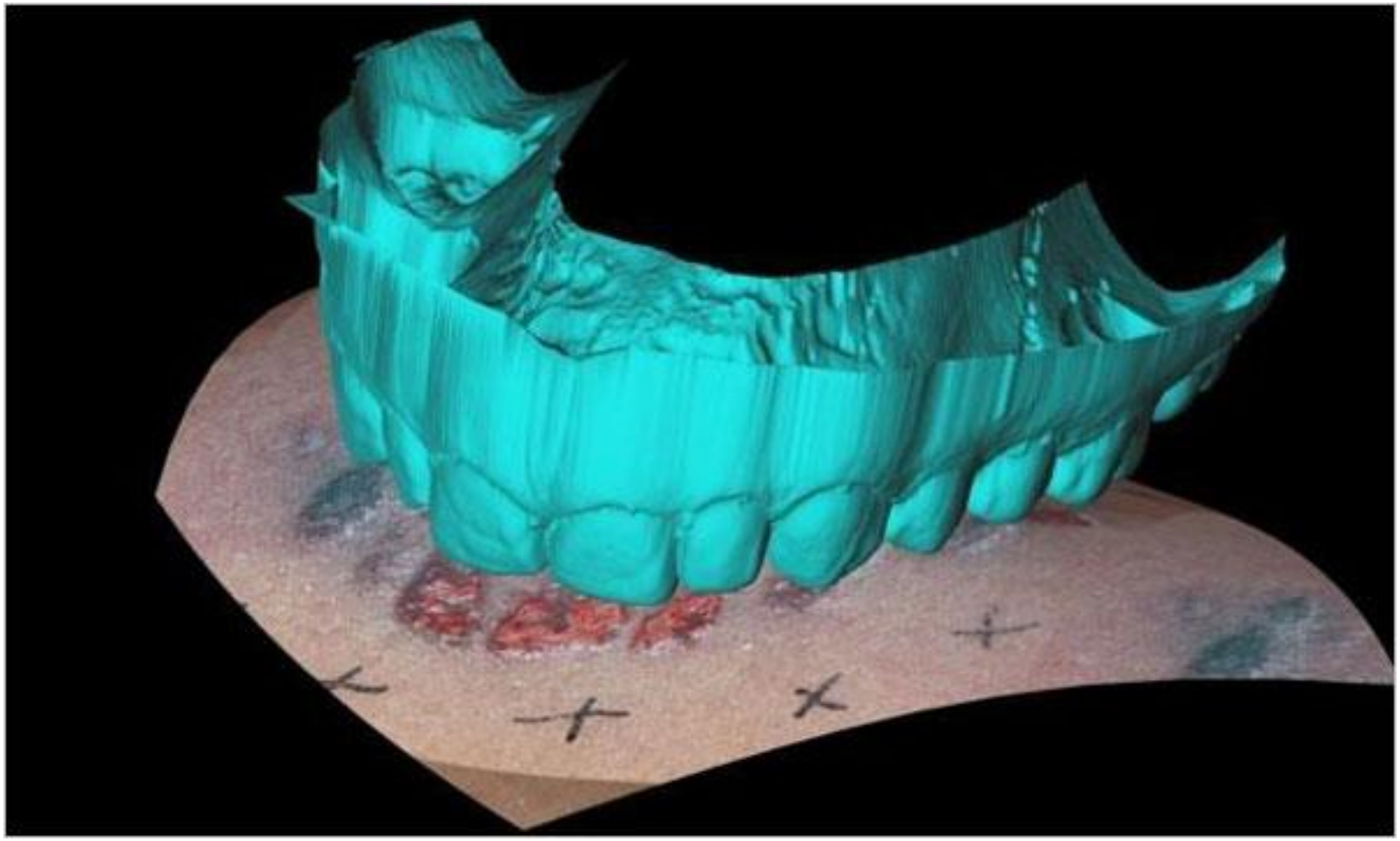
NATIONAL COMMISSION ON FORENSIC SCIENCE

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

Recommendations to the Attorney General Regarding Use of the Term "Reasonable Scientific Certainty"

- There is no common definition within science disciplines as to what threshold establishes "reasonable" certainty. Therefore, whether couched as "scientific certainty" or "[discipline] certainty," the term is idiosyncratic to the witness.
- The term invites confusion when presented with testimony expressed in probabilistic terms. How is a lay person, without either scientific or legal training, to understand an expert's "reasonable scientific certainty" that evidence is "probably" or possibly linked to a particular source?

Technically complicated but unreliable testimony is routinely used as evidence in criminal prosecutions




EXPERT LIAR

Causation is often confused with diagnosis

- A diagnosis can be seen
  - X-rays, MRI, CT
  - Surgical/ autopsy
  - **There is direct evidence** of diagnosis that the jury can see
- A cause cannot be seen
  - Always based on inference
  - **There is only circumstantial evidence** of causation that the jury can't see

A diagnosis is based on observation

Determination of “most probable” cause is based on comparison of risk

Risk is the chance of something happening in the future, based on how often it has happened in the past

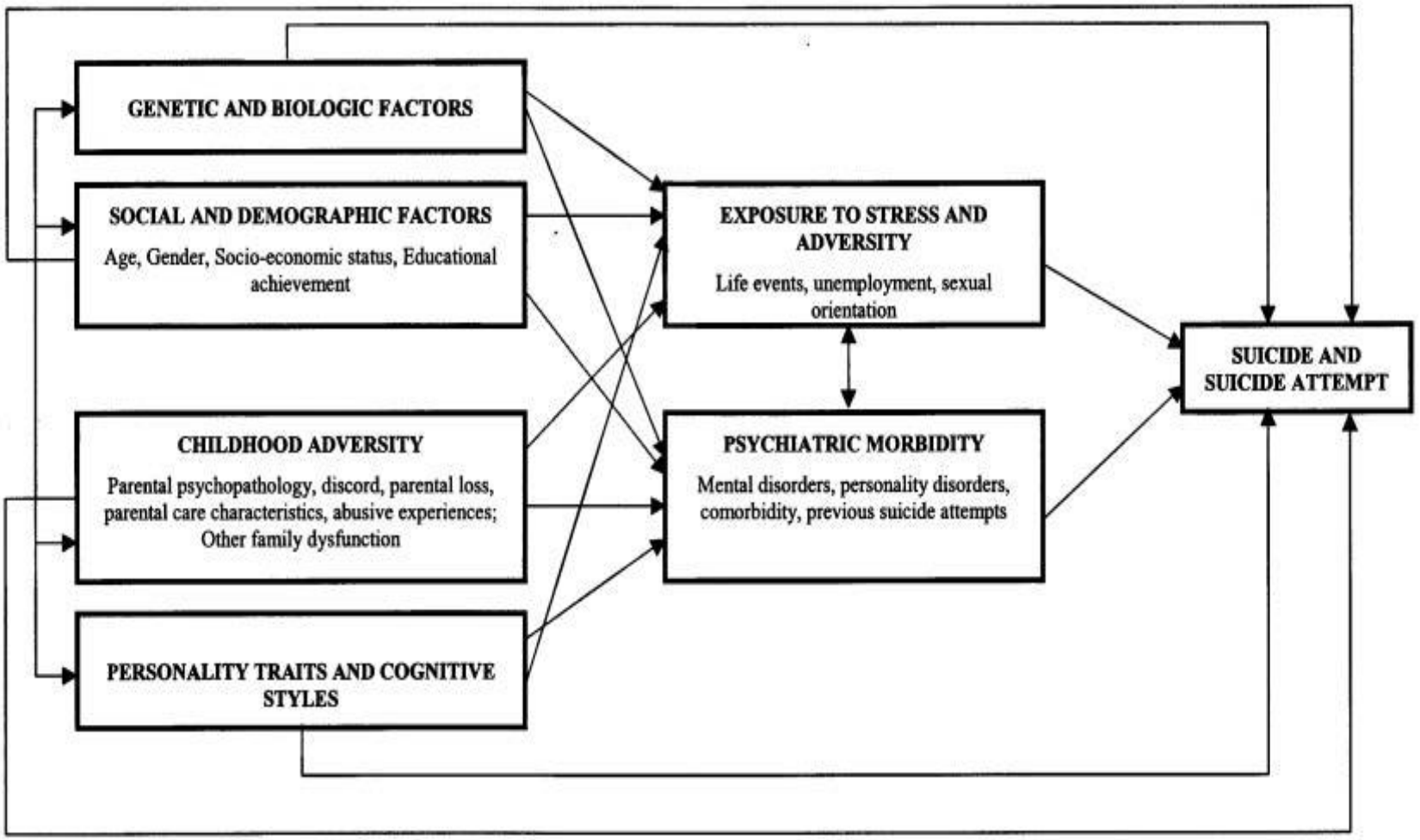
Where does risk come from?

Who is more likely to have a heart attack tomorrow?

Medicolegal causation of psychiatric outcomes

- Required for legal actions associated with violent events that follow exposures to potential triggers
  - homicide, assault, and suicide
- Suicide is multifactorial
  - commonly related to alleged drug errors
- Teen suicide is *multi*-multifactorial
  - Opportunity for triggers is high

Teen suicide causal factors



Beautrais A. Suicide in New Zealand II: a review of risk factors and prevention. N Z Med J. 2003;116(1175):U461.

The *legal* causation question in a suicide is really an *epidemiologic* causation question

What is the chance of the suicide occurring *but-for* the harmful exposure?

What is the *risk* of the injury in the presence of the harmful exposure?

What is the *risk* of the injury in the absence of the harmful exposure?*

This ratio is called a "relative risk"

Integration of epidemiologic causation into US case law on injury causation

- US Court of Appeals opinion in 2016 that sets forth the generally accepted methodology for assessing injury causation
- Discussed a "3-step" process of injury causation
  - Described the use of epidemiologic methods for injury causation for the first time

FILED
United States Court of Appeals
Tenth Circuit

July 19, 2016

Elisabeth A. Shumaker
Clerk of Court

PUBLISH

UNITED STATES COURT OF APPEALS

FOR THE TENTH CIRCUIT

DONALD L. ETHERTON,

Plaintiff - Appellee,

v.

OWNERS INSURANCE COMPANY,

Defendant - Appellant.

No. 14-1164

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO
(D.C. No. 1:10-CV-00892-PAB-KLM)

Gregory R. Giometti (Amanda Burke, with him on the briefs), Gregory R. Giometti & Associates, P.C., Denver, Colorado, appearing for Defendant-Appellant.

Ethan A. McQuinn (Chad P Hemmat, and Jason G. Alleman, with him on the brief), Anderson, Hemmat & McQuinn, LLC, Greenwood Village, Colorado appearing for Plaintiff-Appellee.

Before **HARTZ**, **GORSUCH**, and **MATHESON**, Circuit Judges.

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[3]Dr. Ramos cited a number of articles and textbooks in support of his methodology. *See* Docket No. 48 at 24-27 (citing Randall L. Braddom, Physical Medicine & Rehabilitation 110 (4th ed. 2010); Michael D. Freeman, Christopher J. Centeno & Sean S. Kohles, *A Systematic Approach to Clinical Determinations of Causation in Symptomatic Spinal Disk Injury Following Motor Vehicle Crash Trauma*, 1 Physical Medicine & Rehabilitation 951 (October 2009); American Medical Association Guides to the Evaluation of Permanent Impairment 224 (6th ed. 2007); American Medical Association Guides to the Evaluation of Disease & Injury Causation (J. Mark Melhorn & William E. Ackerman eds., 1st ed. 2007); Samuel McLean, David Williams & Daniel Clauw, *Fibromyalgia After Motor Vehicle Collision: Evidence & Implications*, 6 Traffic Injury Prevention 97 (June 2005)).

The 3 elements of a causal analysis of injury are:

1. Plausibility

   Hill criteria

   Risk of injury given the event (if known)

2. Temporality

   Sequence, proximity and latency

3. Lack of a more likely alternative explanation

   Risk of same condition at same time, given pre-event condition of individual, but if the event hadn't occurred

$$\mathrm{RR} = \frac{\mathrm{p}(O \mid E)}{\mathrm{p}(O \mid \bar{E})}$$

Etherton steps applied to a novel teen suicide investigation

- 17 year old male, senior in high school
  - "Boy Scout"
- No known risk factors
- Presented to pediatrician for hand pain and sinus infection
- Prescribed cefprozil (500 mg b.i.d.) and ketorolac (10 mg, t.i.d.)
- The pharmacy mis-dispensed ***isosorbide mononitrate*** instead of the ketorolac
- 29 hours after taking the first dose of the organic nitrate the boy shot himself with a hunting rifle in his parents' bedroom

First step: Plausibility

- *Can* isosorbide mononitrate cause suicidal behavior?
  - If so, how often (risk)?
- Review of world literature for studies of suicidality among healthy teenagers given a drug for older patients with angina
- Application of Hill causal criteria
  - Coherence, analogy, biologic plausibility, specificity
- Analogy
  - Any psychiatric effects in any age group

Visual hallucinations and suicidal ideation attributed to isosorbide dinitrate

Randolph Rosenthal, M.D.

Since its introduction, the long-acting vasodilator isosorbide dinitrate has gained wide acceptance in the management of appropriate cardiovascular conditions. Not surprisingly, the widespread use has led over the years to some reports[1-3] of side effects. This article calls attention to a hitherto unreported* serious psychiatric symptom complex that could be potentially life threatening and was rapidly relieved by drug discontinuation.

Case report

An 87-year-old woman was persuaded to seek psychiatric consultation when she confided to her daughter that she intended to discontinue all her cardiac life-support medications as a way of ending her life. She explained to her daughter that she was depressed about the recent occurrence of visual hallucinations, as she believed them to herald the onset of senility. She was firm in her resolve that she would rather be dead than "senile."

During the interview, her appearance was that of a neat and clean individual, appropriately well groomed and dressed. The sensorium was clear. She was fully oriented to time, place, and person. Memory for remote events was intact. She reported that memory for recent events was good but somewhat less sharp than in years past. However, it obviously was within normal limits for her age. Her attention was keen, and her responses were pertinent. In response to questioning she revealed that she was an avid reader and needed glasses only for reading. A recent ophthalmologic examination had revealed no significant detectable changes in distance or reading vision.

She was obviously distressed and depressed, in appropriate relationship to the thought content that was the basis for her agreeing to seek the consultation. She related that she lived alone in her apartment and walked at least ten blocks each day to the supermarket. Daily trips were necessary because she could not carry more than one day's supply that distance back to the apartment. She said that she was under the care of her family physician. At his direction she was taking digoxin, furosemide, and isosorbide dinitrate, known to her only by its manufacturer's trademark of Isordil.

She had been doing well on this regimen until six weeks prior to the present, when she began to develop visual hallucinations involving her husband, who had died six years earlier, followed by her fears of senility and by feelings of hopelessness and depression. Convinced that she was on a precipice from which there was no escape, she therefore determined to end her life by discontinuing her life-support medications. She was firm-

Dr. Rosenthal is assistant professor of clinical psychiatry at SUNY, Stony Brook, N.Y. Reprint requests to Dr. Rosenthal at 106 Willow Rd., Woodmere, NY 11598.

FDA AERS analysis

- Proportional reporting ratio evaluation
  - Examine the frequency of reported suicidality attributed to isosorbide nitrates relative to all other drugs in the FAERS
- Results
  - Isosorbide nitrate was primary suspect drug ***6.4 times more often*** than all other drugs, averaged together (PRR 6.40, 95% CI; 3.41, 11.98)

S. J. Evans, P. C. Waller, and S. Davis, "Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports.," *Pharmacoepidemiol. Drug Saf.*, vol. 10, no. 6, pp. 483–6.

Naranjo scale

Table I. *ADR probability scale*

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

	Yes	*No*	*Do not know*	*Score*
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

Naranjo *et al.*, "A method for estimating the probability of adverse drug reactions," *Clin. Pharmacol. Ther.*, vol. 30, no. 2, pp. 239–245, 1981

Naranjo algorithm

March 23, 2020 - 14:45

Isosorbide mononitrate and teen suicide

1. Are there previous conclusive reports on this reaction?	: Yes	[+1]
2. Did adverse event appear after the suspected drug was given?	: Yes	[+2]
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	: N/K or N/D	[0]
4. Did the adverse reaction appear when the drug was readministered?	: N/K or N/D	[0]
5. Are there alternative causes that could have caused the reaction?	: N/K or N/D	[0]
6. Did the reaction reappear when a placebo was given?	: N/K or N/D	[0]
7. Was the drug detected in any body fluid in toxic concentrations?	: Yes	[+1]
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	: N/K or N/D	[0]
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	: N/K or N/D	[0]
10. Was the adverse event confirmed by any objective evidence?	: Yes	[+1]

Score: 5
Probable ADR

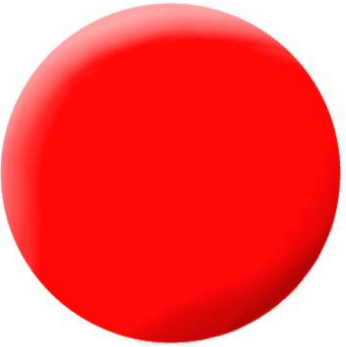
Naranjo algorithm: A method for estimating the probability of adverse drug reactions | pmidCALC online calculators. http://www.pmidcalc.org/?sid=7249508&newtest=Y.

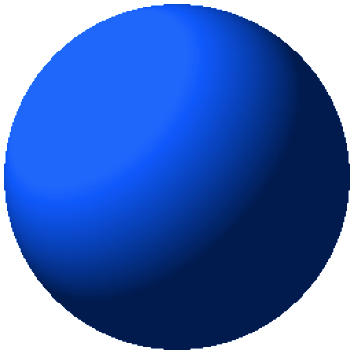
Step 1: Plausibility conclusions

- It is *plausible* that the decedent's suicide resulted from the effects of the isosorbide mononitrate
- The degree of increased risk is unknown, however

Step 2: Temporality

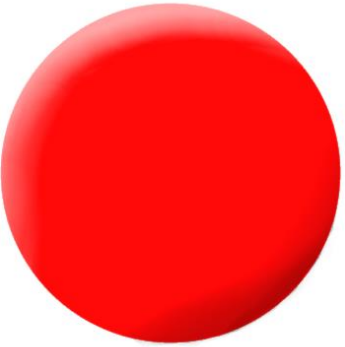
Temporal proximity is the most potent measure of causality

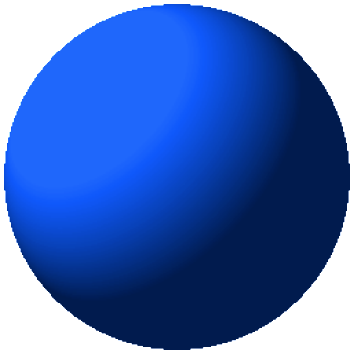




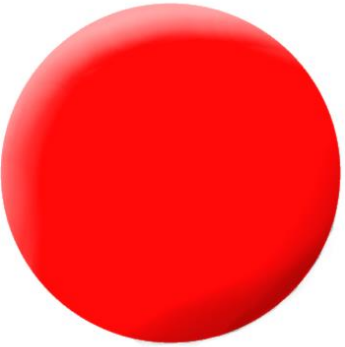
Did the red ball *cause* the blue ball to move?

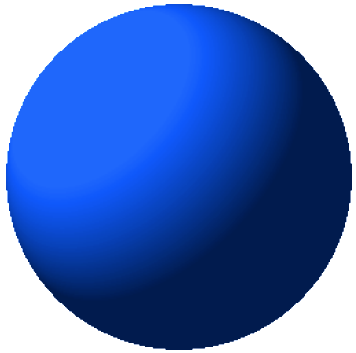
How about now?





Now?





Temporal factors

- Proximity
  - Were the suicidal actions within a reasonable timeframe relative to the effects of the drug?
- Sufficiency
  - Was there enough time for the drug to act to cause the suicidal actions?

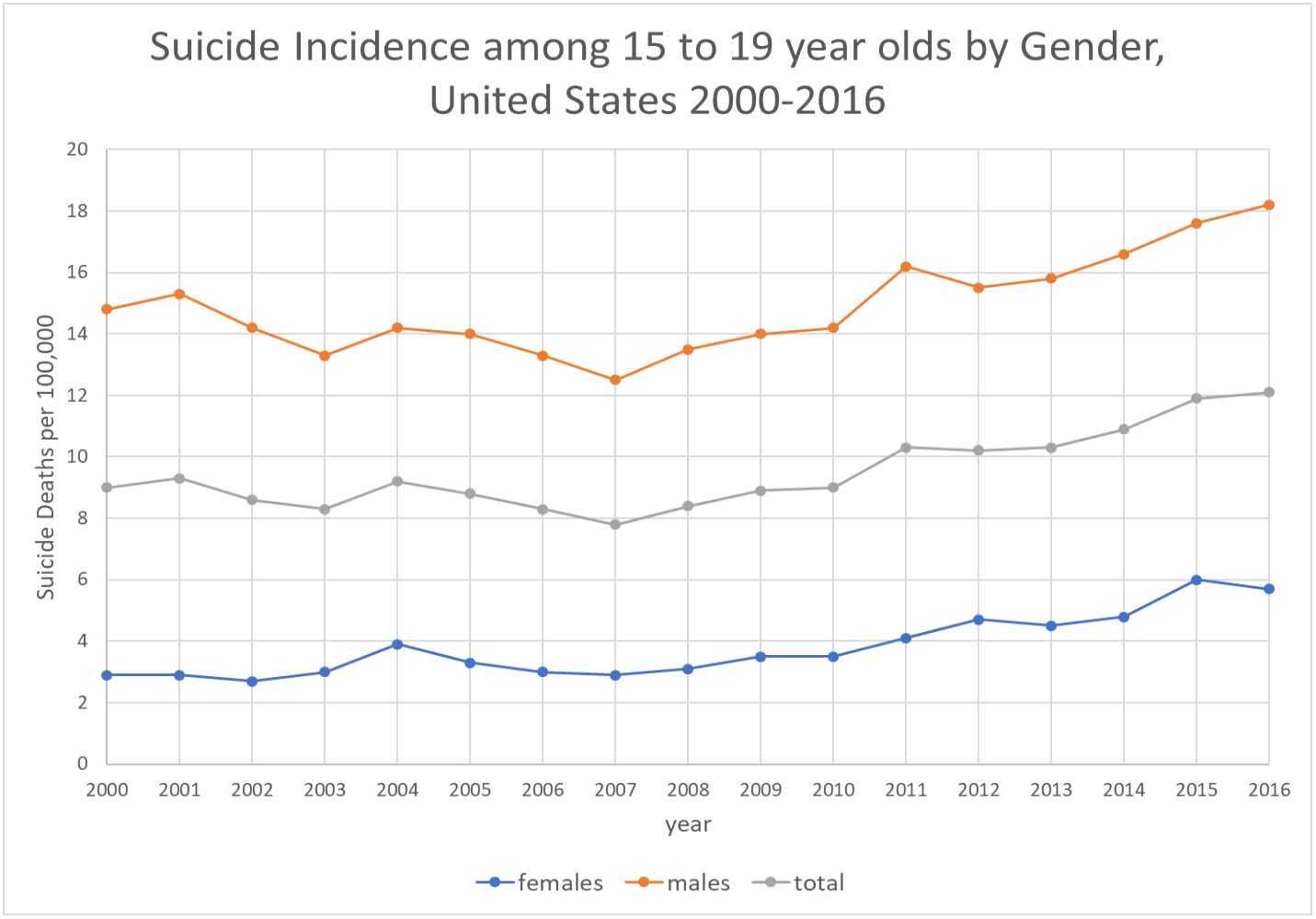
Thadani *et al.*, "Isosorbide-5-mononitrate in angina pectoris: plasma concentrations and duration of effects after acute therapy.," *Clin. Pharmacol. Ther.*, vol. 42, no. 1, pp. 58–65, Jul. 1987

Step 2: Temporality conclusions

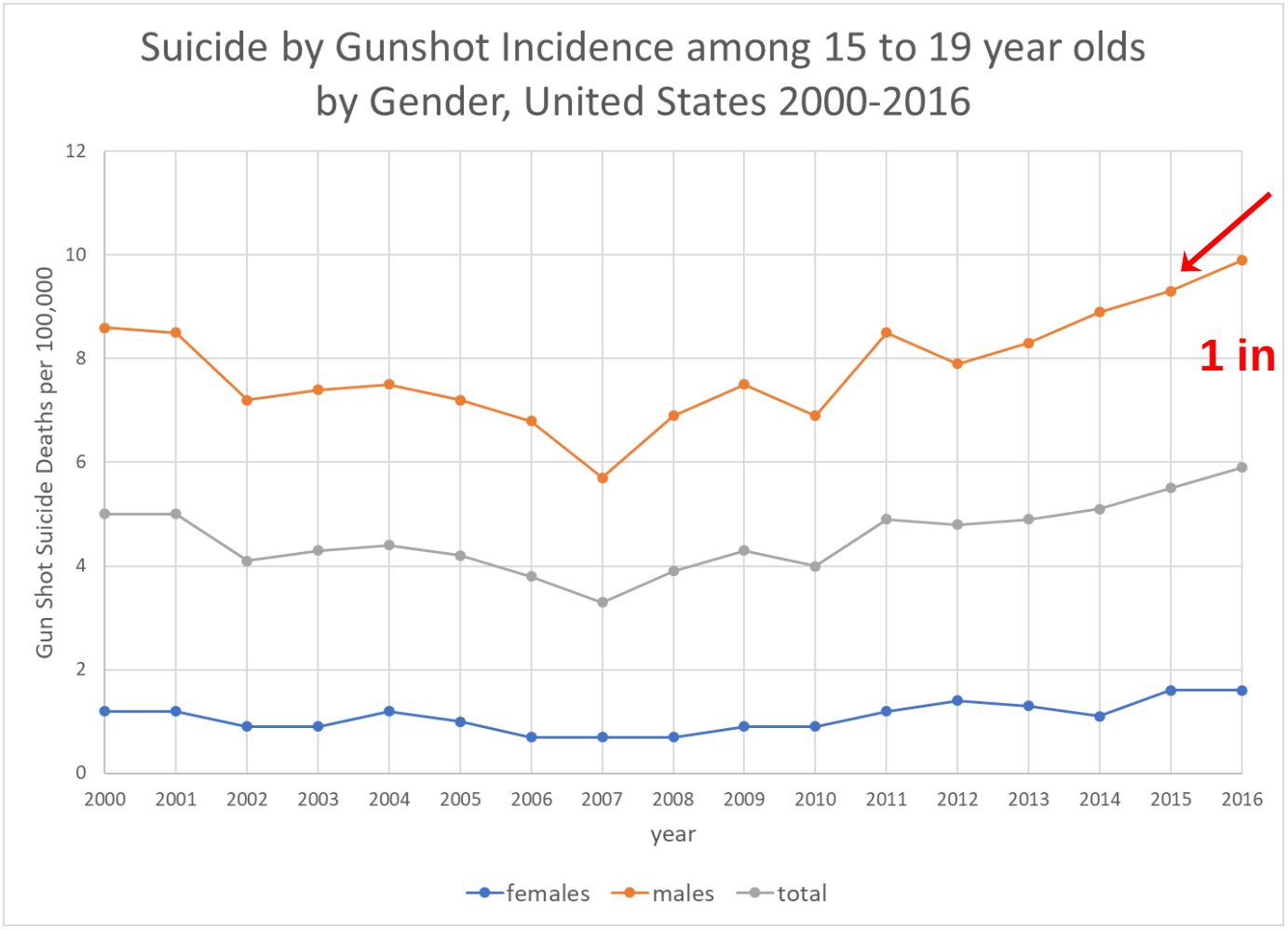
The temporal relationship between the suicide and first dose (29 hours) and last dose (2-3 hours) is both proximate and sufficient

Step 3: Alternative causes

- The assessment from Step 2 is used to evaluate the risk of competing causes, given the **timing** between the medication initiation and the discovery of the suicide
  - What was the chance the decedent would spontaneously become suicidal within a day of taking the drug, but in the absence of the drug?
- There were no known competing risk factors for suicide, aside from demographic predictors



Centers for Disease Control and Prevention, Multiple Cause of Death Data. https://wonder.cdc.gov/mcd.html



Centers for Disease Control and Prevention, Multiple Cause of Death Data. https://wonder.cdc.gov/mcd.html

Step 3: Alternative cause conclusions

- The timeframe of interest was 1 day between initiation of drug and suicide
- Annual risk of 1 in 10,753 equates to a daily risk of 1 in 2,008,000 per day
- Lack of known social, personality, or life stressor factors put decedent in lowest 10% of risk (<1 in 20 million/ day)
  - There were only 11 million male teens 15-19 in US

Causal analysis conclusions

- The lack of established risk for drug exposure is not a barrier to a causal analysis if there are no plausible competing causes
- Probable competing daily risk of <1 in 20 million makes any explanation other than the mis-dispensed drug implausible
- Therefore, the isosorbide mononitrate was not only the most likely (>50%) cause of the suicide, it was the only known cause

Contents lists available at ScienceDirect

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Forensic Pathology

Forensic epidemiologic analysis of the cause of an unexpected teen suicide following ingestion of mis-dispensed isosorbide mononitrate

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ARTICLE INFO

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3-step causation
Forensic epidemiology
Isosorbide mononitrate

ABSTRACT

A 17 year-old previously healthy male committed suicide approximately 1 day after ingesting isosorbide mononitrate, an organic nitrate drug used to treat symptoms of coronary artery disease. The drug had been mis-dispensed by a pharmacy in place of a prescribed anti-inflammatory. In the presented case study, a 3-step probabilistic causal analysis was used to evaluate the most likely cause of the suicide, suitable for presentation in a legal setting as evidence of causation on a more probable than not (> 50 % probable) basis.

1. Case presentation

The decedent was a previously healthy 17 year-old male, who presented to his pediatrician with a 1-month history of nasal congestion associated with a nonproductive cough, sore throat, headache, fever and a thick nasal discharge. He also complained of a 3-week history of right-hand pain. Physical examination findings included irritated and swollen nasal mucosa with a green-yellow discharge. The pediatrician diagnosed acute sinusitis and prescribed a cephalosporin antibiotic (Cefprozil 500 mg, twice per day) and a nonsteroidal anti-inflammatory drug for the hand pain (ketorolac 10 mg, three times per day). The prescriptions were transmitted electronically to a local branch of a chain pharmacy.

consistent with contact with a trigger. The police report concluded that the death was an intentional suicide.

Four day after the death a forensic autopsy was performed on the decedent, which demonstrated an intraoral gunshot entry wound with soot on the anterior surface of the tongue. The projectile was observed to extend upward and to the left. There was complete disruption of the skull and ejection of the brain such that the bones were received separately as well as most of the brain, which was received in small fragments. There was disruption of the face and calvarium. The remainder of the autopsy findings were unremarkable. The medical examiner deemed the manner of death to be suicide, 10 days after the autopsy was performed.

Approximately two months after the autopsy, post mortem blood,

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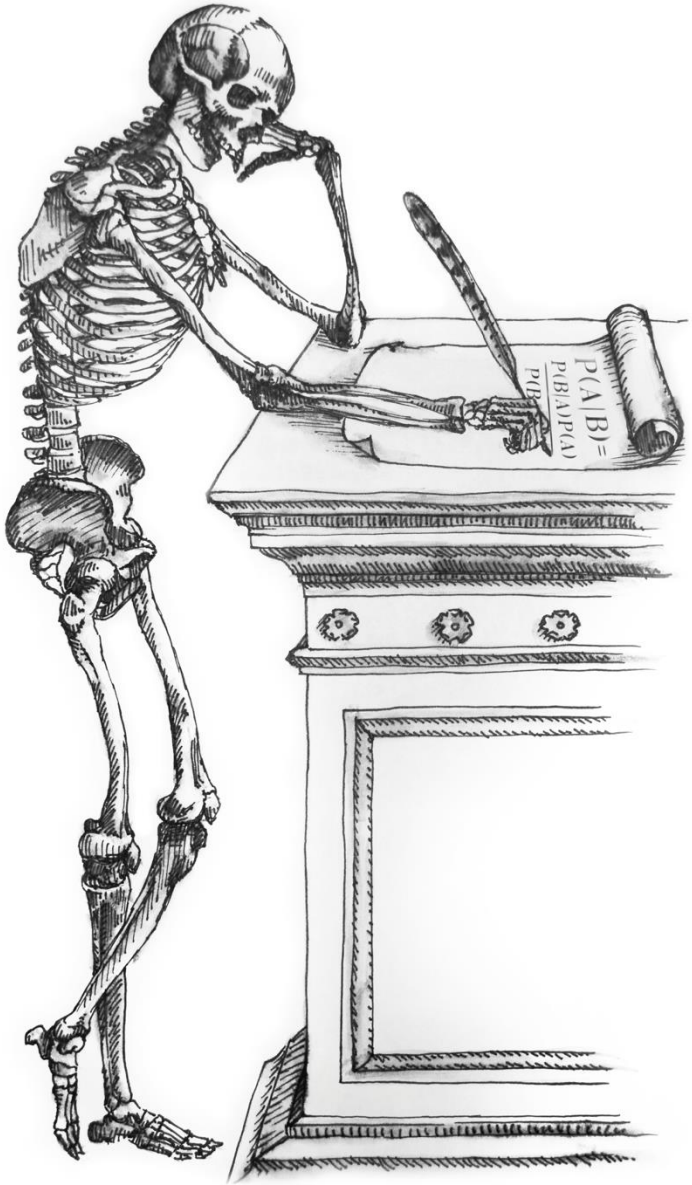

Questions?

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